Zinc Supplement Use and Risk of Prostate Cancer

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The high concentration of zinc in the prostate suggests that zinc may play a role in prostate health. We examined the association between supplemental zinc intake and prostate cancer risk among 46 974 U.S. men participating in the Health Professionals Follow-Up Study. During 14 years of follow-up from 1986 through 2000, 2901 new cases of prostate cancer were ascertained, of which 434 cases were diagnosed as advanced cancer. Supplemental zinc intake at doses of up to 100 mg/day was not associated with prostate cancer risk. However, compared with nonusers, men who consumed more than 100 mg/day of supplemental zinc had a relative risk of advanced prostate cancer of 2.29 (95% confidence interval = 1.06 to 4.95; P_{trend} = .003), and men who took supplemental zinc for 10 or more years had a relative risk of 2.37 (95% confidence interval = 1.42 to 3.95; P_{trend}<.001). Although we cannot rule out residual confounding by supplemental calcium intake or some unmeasured correlate of zinc supplement use, our findings, that chronic zinc oversupply may play a role in prostate carcinogenesis, warrant further investigation. [J Natl Cancer Inst 2003;95:1004–7]

Approximately 15% of the U.S. population uses dietary supplements that contain zinc *(1).* Ten percent of men who take zinc supplements have an average daily zinc intake that is 2–3 times the recommended dietary allowance of 11 mg/day for men *(2).* The reasons why individuals take supplemental zinc are not well documented.

The concentration of zinc in the prostate is higher than that in any other soft tissue in the body *(3).* Zinc levels in prostate adenocarcinoma are markedly lower than those in the surrounding normal prostate tissues *(3).* Several findings that link zinc with the suppression of prostate cancer cell growth *(4–6)* and inhibition of prostate tumor cell invasion *(7,8)* suggest that high intraprostatic zinc levels may protect against prostate carcinogenesis. However, results of other studies suggest that high intraprostatic zinc concentrations may adversely affect prostate cancer risk. For example, zinc enhances the activity of telomerase *(9),* an enzyme thought to be responsible for unlimited proliferation of tumor cells and whose activity is increased in prostate cancer *(10).* Zinc has also been found to antagonize the potential inhibitory effect of bisphosphonates on prostate tumor cell invasion *(11).*

Whether dietary zinc intake affects intraprostatic zinc levels is unknown. However, ingestion of 150 mg/day or more of zinc has undesirable metabolic effects, such as immune dysfunction *(12)* and impaired antioxidant defense *(13),* that are potentially related to prostate cancer. In animal studies, subtoxic zinc levels at doses of 200 parts per million of zinc in supply water may interfere with a cancer-protecting activity associated with selenium intake *(14).* In humans, zinc intake is positively correlated with circulating levels of insulin-like growth factor-I *(15)* and testosterone *(16),* growth factors that are directly related to prostate carcinogenesis. Thus, results of studies that have addressed the systemic effects of dietary zinc suggest that high zinc intakes may be positively associated with prostate cancer risk *(12–16).* To address this issue, we examined the relationship between supplemental zinc intake and prostate cancer risk among participants in the Health Professionals Follow-Up Study. The Health Professionals Follow-Up Study was initiated in 1986, when 51 529 U.S. male health professionals aged 40 to 75 years responded to a mailed questionnaire concerning their medical history and disease risk factors. Since then, follow-up questionnaires have been mailed biennially to cohort members to update information on newly diagnosed illnesses. The Health Professionals Follow-Up Study was approved by the institutional review board on the use of human subjects in research of the Harvard School of Public Health.

Dietary intake was assessed in 1986 with the use of a 131-item semiquantitative food-frequency questionnaire that requested detailed information on the amount and duration of supplement use, including questions on the brand of multivitamin used and the use of vitamins A, C, and E, zinc, iron, and calcium. The Pearson correlation coefficient between zinc intake reported in this questionnaire and in two 1-week dietary records was 0.71 *(17),* indicating reasonable validity of our questionnaire-based assessment of zinc intake. On each follow-up questionnaire, participants were asked to report whether they had been diagnosed with prostate cancer during the previous 2 years. We requested permission from men who reported a prostate cancer diagnosis (or from the next of kin for decedents) to obtain medical records and pathology reports, which were used to confirm the diagnosis and to determine the stage of the cases of prostate cancer. Multivariable relative risks (RRs) were computed using the Cox proportional hazards model *(18).* The proportional hazards assumption was satisfied. All statistical tests were two-sided.

During 587 444 person-years of follow-up, we documented 2901 new cases of prostate cancer. Among the men in our study population, supplemental zinc provided 32% of total zinc intake and thus represented by far the major source of zinc. Other sources of zinc included beef and breakfast cereals, which provided 11% and 5%, respectively, of zinc intake. The median value of the highest

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category of supplemental zinc intake (reported by approximately 1% of the study population) was 143 mg/day, a dose that exceeds the current recommended dietary allowance by 13-fold. We examined supplemental zinc use in relation to various risk factors for prostate cancer (Table 1). Compared with nonusers, men who consumed supplemental zinc also consumed more multivitamins, supplemental calcium, supplemental vitamin E, lycopene, copper, iron, folate, and fish, but had lower intakes of red meat, and were slightly less likely to have had a history of prostate-specific antigen screening.

We next examined the association between supplemental zinc use and prostate cancer risk (Table 2). In age-adjusted and multivariable models, we observed no statistically significant associations between supplemental zinc intakes at doses less than or equal to 100 mg/day and the risk of prostate cancer. However, compared with nonusers of zinc supplements, men who consumed more than 100 mg/day of supplemental zinc had a multivariable RR of advanced prostate cancer of 2.29 (95% confidence interval [CI] = 1.06 to 4.95; P_{trend} = .003). By contrast, zinc obtained from food sources was not associated with prostate cancer risk (data not shown). We also examined the association between duration of supplemental zinc and the risk of prostate cancer (Table 2). Increasing duration of supplemental zinc use was unrelated to the risk of total or organ-confined prostate cancer. However, the multivariable RR of advanced prostate cancer for men who used supplemental zinc for 10 years or longer compared with nonusers was 2.37 (95% CI = 1.42 to 3.95; P_{trend}<.001).

Apart from chance, possible explanations for these findings are residual confounding by supplemental calcium intake or by some unmeasured correlate of zinc supplement use. We examined these possibilities in various subanalyses by restricting our study population to men who reported supplemental calcium intakes of less than 900 mg/day, by adjusting for intakes of copper, iron, and folate; by controlling for benign prostatic hyperplasia; and by excluding nonusers of zinc supplements. The results were essentially unchanged. Because zinc has long been associated with prostate health, the observed associations may also reflect the effects of self-medication of longstanding prostate symptoms with surplus amounts of supplemental zinc. In addition, increased zinc supplement use may have coincided with decreased medical surveillance, which could ultimately have resulted in late detection of prostate cancer and, thus, a greater probability of advanced prostate cancer in these men. However, accounting for history of prostate-specific antigen screening and excluding the early years of follow-up did not materially alter the results. In summary, we found that excessively high supplemental zinc intake was associated with an increased risk of advanced prostate cancer. Strong evidence to support a specific mechanism for this association is lacking at present. Nevertheless, our findings suggest that the role of chronic oversupply of zinc in prostate carcinogenesis requires further investigation.

Table 1. Selected characteristics of 46 974 participants in the Health Professionals Follow-Up Study in relation to level of supplemental zinc intake at baseline*

Characteristic	Level of supplemental zinc intake, mg/day†				
	Nonusers	1–24	25–74	75–100	⩾101
Median supplemental zinc intake, mg/day‡	0	10	44	82	143
No. of participants	35 121	7479	3117	845	412
Age in 1986, y (mean ± SD)	54 ± 9.7	55 ± 9.8	56 ± 9.5	56 ± 9.1	56 ± 9.3
Body mass index in 1986, kg/m^2 (mean ± SD)	26 ± 3.4	25 ± 3.1	25 ± 3.1	25 ± 3.2	26 ± 3.7
Body mass index at age 21, kg/m^2 (mean ± SD)	23 ± 3.1	23 ± 3.1	23 ± 3.1	23 ± 3.2	23 ± 3.7
Family history of prostate cancer, %	12	12	11	11	12
History of type II diabetes, %	3	3	3	3	4
Routine screening for PSA by 2000, %	78	79	80	75	74
Smoked in the past 10 y, %	22	21	20	20	20
Vigorous physical activity (mean METs ± SD)	12 ± 26	14 ± 24	16 ± 31	16 ± 28	16 ± 28
Multivitamin use, %	26	96	84	83	87
Mean intakes (±SD)					
Supplemental calcium, mg/day	37 ± 150	168 ± 267	323 ± 376	584 ± 559	1021 ± 700
Supplemental vitamin E, mg/day	40 ± 128	144 ± 216	316 ± 269	326 ± 298	465 ± 315
Zinc from food sources, mg/day§	13.2 ± 4.1	13.3 ± 5.7	13.2 ± 7.0	13.3 ± 3.9	13.3 ± 2.9
Lycopene, μg/day§	10 312 ± 7411	10 374 ± 7832	10 759 ± 7541	11 052 ± 7545	10 982 ± 7816
α-Linolenic acid, g/day§	1.1 ± 0.36	1.1 ± 0.36	1.1 ± 0.35	1.1 ± 0.35	1.1 ± 0.35
Fructose, g/day§	49.0 ± 17.3	49.7 ± 17.9	50.0 ± 18.0	49.5 ± 18.1	49.6 ± 18.1
Total calcium, mg/day§	829 ± 348	984 ± 420	1169 ± 549	1445 ± 747	1919 ± 872
Copper, mg/day§	1.6 ± 0.4	2.9 ± 1.3	2.8 ± 1.8	2.5 ± 1.6	2.8 ± 1.6
Iron, mg/day§	15.7 ± 9.2	29.3 ± 15.6	35.3 ± 27.1	32.2 ± 25.8	44.7 ± 34.1
Folate, μg/day§	425 ± 218	583 ± 273	763 ± 413	793 ± 474	892 ± 485
Fish, servings/wk	2.3 ± 2.0	2.5 ± 2.1	2.8 ± 2.3	2.9 ± 2.3	2.9 ± 2.7
Red meat, servings/wk‖	6.9 ± 4.9	6.4 ± 4.8	5.5 ± 4.5	5.7 ± 4.7	5.8 ± 5.0

*All values (except age) are standardized to the age distribution of the study population. PSA = prostate-specific antigen; METs = metabolic equivalents per week.

†Specific information on the form of supplemental zinc was not available. However, for zinc supplements, the most common form is zinc gluconate.

‡Maximum value of highest category of supplemental zinc intake level is 270 mg/day.

§Nutrients are adjusted for total energy intake.

‖Red meat includes beef, pork, lamb, hamburgers, hot dogs, processed meat, and bacon. Servings of beef, pork, or lamb as a main dish were converted to servings as a mixed dish.

Table 2. Relative risk of prostate cancer in relation to level and duration of supplemental zinc intake at baseline among participants in the Health Professionals Follow-Up Study*

Variable	Nonusers	Users				P_{trend}
		Level of supplemental zinc intake, mg/day				
		1–24	*25–74*	*75–100*	*≥101*	
Total prostate cancer						
No. of cases/person-years	2127/440 052	469/93 031	215/38 843	54/10 515	36/5003	
Age-adjusted RR† (95% CI)	1.0 (referent)	0.90 (0.85 to 1.04)	0.99 (0.86 to 1.14)	0.90 (0.69 to 1.18)	1.24 (0.89 to 1.73)	.71
Multivariate RR‡ (95% CI)	1.0 (referent)	0.94 (0.83 to 1.07)	1.01 (0.86 to 1.19)	0.95 (0.71 to 1.26)	1.29 (0.88 to 1.89)	.34
Multivariate RR§ (95% CI)	1.0 (referent)	0.94 (0.83 to 1.07)	1.01 (0.86 to 1.19)	1.02 (0.76 to 1.37)	1.37 (0.94 to 2.01)	.17
Multivariate RR‖ (95% CI)		1.0 (referent)	1.08 (0.91 to 1.29)	1.05 (0.77 to 1.43)	1.43 (0.95 to 2.15)	.10
Organ-confined cancer						
No. of cases	1223	282	108	26	14	
Age-adjusted RR† (95% CI)	1.0 (referent)	0.99 (0.87 to 1.13)	0.87 (0.71 to 1.06)	0.76 (0.51 to 1.12)	0.83 (0.49 to 1.41)	.06
Multivariate RR‡ (95% CI)	1.0 (referent)	0.97 (0.82 to 1.15)	0.88 (0.71 to 1.10)	0.79 (0.52 to 1.19)	0.88 (0.49 to 1.58)	.19
Multivariate RR§ (95% CI)	1.0 (referent)	0.97 (0.82 to 1.15)	0.89 (0.72 to 1.12)	0.84 (0.55 to 1.27)	0.96 (0.53 to 1.72)	.35
Multivariate RR‖ (95% CI)		1.0 (referent)	0.95 (0.75 to 1.21)	0.92 (0.59 to 1.43)	1.10 (0.59 to 2.06)	.89
Advanced cancer						
No. of cases	317	56	40	11	10	
Age-adjusted RR† (95% CI)	1.0 (referent)	0.75 (0.56 to 0.99)	1.23 (0.88 to 1.71)	1.23 (0.68 to 2.25)	2.28 (1.22 to 4.28)	.008
Multivariate RR‡ (95% CI)	1.0 (referent)	0.81 (0.57 to 1.16)	1.45 (0.98 to 2.12)	1.39 (0.72 to 2.71)	2.29 (1.06 to 4.95)	.003
Multivariate RR§ (95% CI)	1.0 (referent)	0.81 (0.57 to 1.15)	1.36 (0.92 to 2.01)	1.68 (0.86 to 3.26)	2.39 (1.12 to 5.11)	.002
Multivariate RR‖ (95% CI)		1.0 (referent)	1.72 (1.11 to 2.69)	1.93 (0.92 to 4.03)	2.91 (1.23 to 6.90)	.002
		Duration of supplemental zinc use, y				
		1–4	*5–9*	*≥10*		
Total prostate cancer						
No. of cases/person-years	2127/440 052	606/118 870	92/16 870	76/11 653		
Age-adjusted RR† (95% CI)	1.0 (referent)	0.96 (0.87 to 1.05)	0.97 (0.78 to 1.19)	1.00 (0.79 to 1.25)		.67
Multivariate RR‡ (95% CI)	1.0 (referent)	0.97 (0.86 to 1.09)	0.95 (0.76 to 1.19)	1.02 (0.79 to 1.32)		.97
Multivariate RR§ (95% CI)	1.0 (referent)	0.97 (0.86 to 1.09)	0.96 (0.76 to 1.21)	1.09 (0.85 to 1.41)		.67
Multivariate RR¶ (95% CI)		1.0 (referent)	0.95 (0.75 to 1.21)	1.05 (0.81 to 1.35)		.93
Organ-confined cancer						
No. of cases	1223	349	49	32		
Age-adjusted RR† (95% CI)	1.0 (referent)	0.97 (0.86 to 1.09)	0.90 (0.68 to 1.20)	0.74 (0.52 to 1.05)		.05
Multivariate RR‡ (95% CI)	1.0 (referent)	0.96 (0.82 to 1.12)	0.86 (0.63 to 1.18)	0.75 (0.51 to 1.09)		.09
Multivariate RR§ (95% CI)	1.0 (referent)	0.96 (0.82 to 1.13)	0.88 (0.64 to 1.21)	0.79 (0.54 to 1.16)		.16
Multivariate RR¶ (95% CI)		1.0 (referent)	0.89 (0.64 to 1.24)	0.77 (0.53 to 1.14)		.89
Advanced cancer						
No. of cases	317	76	18	23		
Age-adjusted RR† (95% CI)	1.0 (referent)	0.80 (0.62 to 1.03)	1.26 (0.79 to 2.03)	2.01 (1.31 to 3.07)		.004
Multivariate RR‡ (95% CI)	1.0 (referent)	0.89 (0.65 to 1.23)	1.53 (0.90 to 2.61)	2.37 (1.42 to 3.95)		<.001
Multivariate RR§ (95% CI)	1.0 (referent)	0.88 (0.64 to 1.22)	1.47 (0.86 to 2.54)	2.56 (1.54 to 4.26)		<.001
Multivariate RR¶ (95% CI)		1.0 (referent)	1.44 (0.81 to 2.56)	2.55 (1.49 to 4.32)		<.001

*Total prostate cancer: we excluded stage T1a lesions (3% or less of the total) because stage T1a lesions are typically indolent and are especially prone to detection bias. Organ-confined cancers are those with no evidence of extraprostatic involvement at time of diagnosis; advanced cancers are those extending regionally to the seminal vesicle or other adjacent organs, pelvic lymph nodes, or distal organs (usually bone) at the time of diagnosis; or that were fatal by the end of follow-up. The sum of organ-confined prostate cancer cases and advanced prostate cancer cases does not equal the number of total prostate cancer cases because data on stage was not available for all cases and because we excluded stage T3a cancers in the organ-confined and the advanced categories because they are neither organ-confined nor are they usually advanced and hence do not fall into either group. RR = relative risk; CI = confidence interval.

†RR (95% CI) adjusted for current age.

‡RR (95% CI) adjusted for current age, time period (1986–1988, 1988–1990, 1990–1992, 1992–1994, 1994–1996, 1996–1998, 1998–2000), body mass index at age 21, height at baseline in 1986, pack-years of smoking in the previous decade, family history of prostate cancer, vigorous physical activity, regular aspirin use, intake of total energy, dietary calcium, supplemental calcium, fructose, supplemental vitamin E, tomato-based foods, fish, red meat, and α-linolenic acid.

§Excludes non-case subjects who had not had a prostate-specific antigen (PSA) test by 2000 (19.5% of person-years excluded). This analysis was conducted to examine the possibility that underlying differences in PSA screening behavior according to zinc supplement use affected the likelihood of prostate cancer detection, thereby biasing our results by creating spurious associations.

‖Excludes nonusers of zinc supplements; light users (1–24 mg/day) were the referent group. This analysis was performed to examine the possibility that supplement users differ from nonusers with respect to unmeasured, potentially confounding variables.

¶Excludes nonusers of zinc supplements; brief users (1–4 years) were the referent group. This analysis was performed to examine the possibility that supplement users differ from nonusers with respect to unmeasured, potentially confounding variables.

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NOTES

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